Remarks/Arguments

Claims 22-32 are pending in the subject application. Claim 22 has been amended to recite that the method is for screening kidney function for the ability to fragment proteins and kidney function is correlated to protein fragmentation observed in the urine sample. This amendment is supported by the HPLC data shown in Figures 3, 4, and 6-10, as well as the disclosure at paragraph 75. Claim 25 has been amended to recite that the decrease in fragmentation is correlated with the presence of kidney disease or condition affecting renal function. This amendment is supported by the disclosure at paragraph 76. New claims 34 and 35 are directed to embodiments of the invention wherein either transferrin or IgG fragmentation is analyzed. These claims find support in original claim 32. New claim 33 recites specific diseases or conditions treated with the claimed method. Support for this claim is found at page 13 and in original claim 28. New claim 34 is directed to an embodiment where the protein being ananlyzed is albumin (See Figures for support); according to new claim 35 the protein being analyzed is IgG (See paragraph 53). New claims 36 and 38 are directed to embodiments wherein the patient has a form of diabetes and the protein that is analyzed is albumin. Support for these claims is found throughout the specification. New claim 37 is directed to an embodiment where the fragmentation profile is generated by HPLC, as demonstrated in the figures. Other amendments to the claims are nonsubstantive in nature. Accordingly, no new matter is added by these amendments to the claims.

I. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 22, 23 and 25-32 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner asserts that the specification does not provide written description support for the breadth of the claims. This rejection is respectfully traversed as follows.

The claims, as amended, are directed to methods of screening kidney function in a patient, specifically the ability of the kidney to fragment proteins. It is known in the art that protein is filtered from the blood by the kidneys and excreted in the urine. It is also known that the kidneys fragment protein during filtration, resulting in a specific fragmentation profile for each filtered protein. Kidney-filtered proteins are processed by two distinct cellular pathways. The major pathway, a high-capacity retrieval pathway, returns most of the filtered protein to the blood supply intact. The protein not taken up by the retrieval pathway is degraded by lysosomes during renal passage and excreted as fragments in urine. Eppel et al., Am. J. Kidney Dis., (2000), 45(3):418-26.

Applicant's previous studies have shown that excreted proteins are generally modified and fragmented as they are filtered through the kidney (See U.S. 6,447,989 and U.S. 6,589,748). Applicant has now discovered that most of the protein in urine is fragmented at predetermined sites within the protein as it is filtered through the kidneys, which results in protein fragments that can be separated to provide a distinct fragmentation profile for any protein in urine. Applicant's studies also show that the tertiary structure of protein, *e.g.*, albumin, is a critical determinant for albumin processing by the kidney and have demonstrated that albumin is metabolized during renal passage and excreted in the urine as a mixture of intact protein and fragments.

Applicant has also demonstrated that the process responsible for albumin fragmentation is similar in diabetic patients with normoalbuminuria (intact albumin represented 0.01-4.0% of total urinary radioactivity). However, there is a reduction in the fragmentation ratio (fragmented:intact protein) in diabetic patients with micro- or macroalbuminuria (intact albumin represented 2.7-55.5%, $P = 0.048$). This change in the fragmentation ratio is directly related to

the degree of albuminuria. These results have important implications for understanding the mechanisms underlying albuminuria in nondiabetic volunteers and type 1 diabetic patients. In nondiabetic volunteers, the renal processing of albumin involves a relatively rapid and comprehensive degradation of albumin to small fragments (range 1-15 kDa). The degradation process is inhibited in diabetic patients, while in healthy individuals the vast majority of filtered protein is fragmented. Further, in individuals whose kidneys are compromised, fragmentation is inhibited, resulting in a higher than normal content of intact and intact modified protein in the urine.

Thus, rather than attempting to detect and quantitate intact protein in a clinical sample, Applicant demonstrates in the present application that the fragment profiles of proteins in urine provide information concerning the state of the patient's health. An alteration in the fragmentation profile of any urinary protein toward larger fragments, and ultimately toward non-fragmented, full-length protein is an indication that kidney function is impaired.

The present specification discloses the claimed invention in detail. The specification teaches how to obtain a fragmentation profile for any urinary protein, and for that matter, protein fragmentation profiles of a variety of proteins were known in the art at the time of the invention. The specification teaches that fragmentation profiles shift away from smaller fragments toward larger fragments and non-fragmented protein as kidney function decreases, and provides sufficient examples of the shift to larger fragments. The mere presence of larger protein fragments in a urine sample indicates that kidney function is not optimal. Thus, the specification provides sufficient written description of the claimed method for determining whether kidney function is normal or abnormal on the basis of observation of fragmentation of urinary proteins. Finally, the specification teaches that an increase in the the presence of intact protein or intact

modified protein (which is defined in the specification as substantially full-length protein) is an indication of kidney malfunction. The specification also teaches that the presence of multiple peaks that appear in the range of full length protein is an indicator of the presence of intact modified protein. (*See* page 17, para. 80).

Accordingly, the rejection of claims 22, 23 and 25-32 under 35 U.S.C. § 112, first paragraph is respectfully traversed.

II. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 22, 23 and 25-32 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled by the specification. The Examiner asserts that the specification does not teach how to analyze fragmentation profiles and fails to teach how to identify "intact modified" protein. The Examiner also asserts that the skilled practitioner cannot carry out the claimed invention without knowledge of the differences between the fragmented proteins and those that are not fragmented by the kidneys. The Examiner also asserts that the skilled practitioner must be able to identify the intact modified proteins in order to carry out the claimed invention.

Applicant respectfully disagrees with the examiner's concusion.

As amended herein, the claimed invention is directed to a method of screening kidney function for the ability to fragment proteins on the basis of protein fragmentation profiles. Applicant has demonstrated (and indeed, it is known in the art) that normally functioning kidneys fragment filtered proteins in a **demonstrably reproducible fashion**. In fact, it is also known that when the kidneys are not functioning due to late stage diabetes or other diseases known to affect the kidney, there is a significant increase in the amount of native protein in the

urine. Skilled practitioners identify the presence of native protein in the urine and rely on its presence as a diagnosis of kidney malfunction.

Applicant has taken the analysis further by having identified the process by which native protein begins to accumulate in the urine. Applicant's studies clearly demonstrate that when kidney function is less than optimal, fragmentation begins to lessen, until eventually, no fragmentation occurs and native protein accumulates in the urine. The specification also teaches that some protein, which elutes in HPLC in the range of native protein, *i.e.*, intact modified protein, may also occur. As discussed above, the specification teaches that intact modified protein is substantially full length and so it migrates (or elutes) with native protein, but due to some modifications, it may appear as multiple peaks in the range of native protein. It is respectfully submitted that the ordinarily skilled practitioner who presently relies on detection of native protein in the urine as an indicator of diabetes, cal also detect the presence of intact modified protein without having knowledge of the cause or characteristics of the modifications (since it elutes in the range of native protein) and is also able to detect a shift in the protein fragmentation profile at an earlier stage, as taught in the subject application. The skilled practitioner does not need to know why the protein is not fragmented and in fact, until Applicant's studies did not know why native protein accumulates in the urine. It is only necessary that the skilled practitioner be able to detect a shift from normal fragmentation to the presence of larger fragments and non-fragmented protein in the urine. The specification teaches how to carry out such analysis, and as such, teaches how to make and use the claimed invention.

Accordingly, the rejection of claims 22, 23 and 25-32 under 35 U.S.C. § 112, first paragraph (enablement) is respectfully traversed.

It is respectfully submitted that the present application is in condition for allowance, an early notification thereof being earnestly solicited.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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